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Safety and efficacy of icatibant self-administration for acute hereditary angioedema

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Summary

We evaluated the efficacy and safety of icatibant self-administration in 15 patients with hereditary angioedema (HAE) types I or III, for 55 acute attacks (mostly severe or very severe). Icatibant self-administration was generally effective: first symptom improvement occurred in 5 min–2 h (HAE type I; $n = 17$) and 8 min–1 h (HAE type III; $n = 9$) for abdominal attacks and 5–30 min (HAE type I; $n = 4$) and 10 min–12 h (HAE type III; $n = 6$) for laryngeal attacks. Complete symptom resolution occurred in 15 min–19 h (HAE type I; $n = 8$) and 15 min–48 h (HAE type III; $n = 9$) for abdominal attacks and 5–48 h (HAE type I; $n = 3$) and 8–48 h (HAE type III; $n = 5$) for laryngeal attacks. No patient required emergency hospitalization. The only adverse events were mild, spontaneously resolving injection site reactions. Patients reported that carrying icatibant with them gave them greater confidence in managing their condition.

Keywords: complement, genetics, human studies, skin (dermatology), therapy/immunology

Introduction

Hereditary angioedema (HAE) is a rare condition, characterized by recurrent and unpredictable episodes of angioedema in one or more body locations, including the gastrointestinal tract, skin and upper airways. HAE attacks are often painful and debilitating; laryngeal attacks are potentially fatal due to the risk of airway obstruction [1–3].

Bradykinin is a key mediator of HAE symptoms [4–6]. Of the three documented types of HAE, each is associated with absent or abnormal components in bradykinin metabolizing pathways. Autosomal-dominant mutations in the *SERPING1* gene result in deficiency (HAE type I) or loss-of-function (HAE type II) of the C1-inhibitor (C1-INH) protein, which acts to inhibit bradykinin production [7,8]. The aetiology of HAE type III appears to be more heterogeneous, with some patients having a gain-of-function mutation in the *F12* gene which encodes factor XII, a coagulation factor that is also integral to bradykinin production [9–11]. Acute attacks of HAE thus coincide with local bradykinin accumulations, leading to vascular bradykinin B_2 receptor activation and local oedema formation [5,6].

Icatibant, a selective bradykinin B_2 receptor antagonist, has been approved in 37 countries worldwide including, since 2008, within the European Union, for the symptomatic treatment of acute attacks of HAE types I and II in adults, based on efficacy and safety data from three Phase III clinical trials [12,13]. Case-study data suggest that acute attacks of HAE type III may also respond to icatibant [14,15], although icatibant is not licensed for this indication.

Besides efficacy and safety, prompt availability of on-demand treatment is an important consideration in optimizing the management of acute HAE attacks [16,17]. This concept has been demonstrated in an open-label study in which self-administered intravenous C1-INH concentrate was shown to improve HAE patients' quality of life [18]. In view of these data and other studies highlighting the potential benefits of self-treating acute attacks, a 2010 HAE international home therapy consensus document recommended that 'every patient with HAE should be considered for home therapy and self-administration training, once the diagnosis of C1-INH deficiency is confirmed', with icatibant 'considered as an alternative to C1-INH for home therapy' [17]. In 2011, icatibant became the only subcutaneous (s.c.) HAE treatment option available for self-administration in Europe and the United States. We describe experience at our centre of icatibant self-administration.

Materials and methods

This open-label, non-comparative prospective study was conducted between January and October 2010, with

Institutional Ethics Committee of Grenoble University Hospital approval, and the informed consent of all patients. Eligible patients were adults with HAE (types I, II or III) who had previously received health-care professional (HCP)-administered icatibant for at least one acute attack. The diagnosis of patients with HAE type III was confirmed according to clinical and laboratory findings and family history/genetic criteria, as described by Vitrat-Hincky *et al.* [19].

Enrolled patients were trained to self-administer a single dose of icatibant (30 mg, 3 ml solution) by s.c. injection in the abdomen; an HCP demonstrated the injection technique, and patients then self-injected a 3 ml saline solution under supervision. Patients then received two syringes of icatibant to carry with them. For subsequent attacks, patients could either self-administer icatibant (without HCP supervision) or request HCP administration. Patients who chose to self-administer were asked to report the attack to the centre on a 24-h telephone line within 1 h of the injection, advised not to stay alone and instructed to call back again for emergency hospitalization if symptoms worsened within 1 h.

For each self-treated attack, patients recorded outcomes in a 21-point questionnaire. A visual analogue scale (VAS) was used to assess abdominal pain severity [0 mm = absent, 10 mm = worst possible pain; patients were instructed to only self-treat severe/very severe abdominal attacks (VAS >5 mm) and upper airway symptoms]. Assessments included times of attack onset, self-injection, start of symptom improvement and complete resolution of symptoms, the presence/absence and severity of injection site reaction (ISR) pain and adverse events. Patients were also asked how icatibant self-administration affected their confidence in the management of their condition. All patients were followed-up by telephone or in person.

Outcomes data are summarized descriptively; no formal statistical analysis was planned and no sample size calculations were performed. '*N*' denotes the number of patients; '*n*' denotes the number of evaluable attacks (i.e. those attacks for which outcomes data were available).

Results

Patients and angioedema attacks

In total, 45 patients (19 HAE type I, one HAE type II, 25 HAE type III) received self-administration training. After training, 19 patients (nine HAE type I, 10 HAE type III) experienced one to 20 acute HAE attacks each that were treated with icatibant. Fifteen patients (seven HAE type I, eight HAE type III) chose icatibant self-administration (at home, at work or elsewhere) for 55 acute attacks. Patient and attack characteristics are summarized in Table 1.

Efficacy of self-administered icatibant

Times between attack onset and icatibant self-administration ranged from 10 min to 72 h (median 2 h; data missing for seven attacks). Times to first symptom improvement following injection ranged between 5 min and 2 h (median 15 min) for all evaluable attacks of HAE type I ($n = 21$) and 8 min to 12 h (median 40 min) for HAE type III ($n = 19$). Complete symptom resolution occurred within 15 min–48 h (median 5 h) for HAE type I ($n = 11$) and 15 min–96 h (median 24 h) for HAE type III ($n = 17$). Individual response times are shown in Figs 1 and 2.

Retreatment with icatibant and rescue medication

Thirty-eight attacks (78% of HAE type I attacks; 62·5% of HAE type III attacks) were treated with a single self-administration of icatibant. One patient with HAE type I was treated at home by an HCP with C1-INH concentrate, 3 h after a single icatibant self-administration (the patient used to have C1-INH concentrate injections at home for long-term angioedema prophylaxis, and the HCP considered that administering the C1-INH concentrate at home would be faster and safer than emergency hospitalization). Fourteen attacks [all severe/very severe: nine abdominal, two

Table 1. Patient and self-treated attack characteristics.

	HAE type I ($N = 7$)	HAE type III ($N = 8$)
Number of females/males	5/2	7/1
Median age, range (years)	38, 20–50	30·5, 20–42
Median age at diagnosis of HAE, range (years)	17, 11–26	25·5, 18–32
Number of attacks treated with icatibant self-administration (%)	23 (100)	32 (100)
Abdominal	18 (78)	11 (34)
Laryngeal	5 (22)	8 (25)
Laryngeal and abdominal	0	9 (28)
Laryngeal and facial	0	3 (9)
Abdominal, laryngeal and facial	0	1 (3)

Most self-treated abdominal hereditary angioedema (HAE) symptoms were assessed by patients as being severe or very severe. *N*: number of patients.

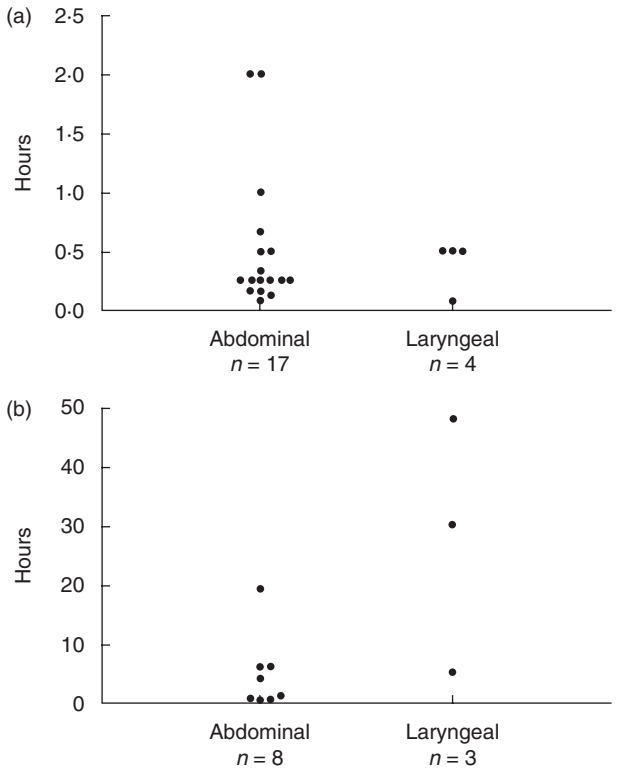

Fig. 1. Individual times to first symptom improvement (a) and complete resolution of symptoms (b) following icatibant self-administration in patients with hereditary angioedema (HAE) type I. Each data point represents one attack of HAE type I; *n*: number of evaluable attacks.

laryngeal, two laryngeal and abdominal, and one facial and laryngeal attack, in five patients (one HAE type I, four HAE type III)] required a second injection of icatibant, 7 h (HAE type I) and 6–9 h (HAE type III) after initial self-administration. Three attacks (one severe laryngeal, and two severe/very severe abdominal attacks, in two patients with HAE type III) needed a third injection of icatibant. All the attacks requiring a second or third icatibant injection showed an initial response, but for some the response was partial after ~6 h ($n = 7$), and for others ($n = 4$) attack recurrence (or worsening) occurred after the initial response (which was positive within 13 min–1 h after the injection but lasted less than 6 h). All patients who required more than one icatibant injection per attack did so consistently for more than one attack.

Safety and tolerability

The only adverse events were local ISRs (including erythema, swelling and itching), reported by 14 patients [for 48 (87%) of the 55 self-treated attacks]. No ISRs occurred for two attacks ($n = 2$). ISRs were generally mild and resolved spontaneously within 0·5–3 h.

Quality of life

The majority of patients (89·4%) reported that carrying syringes of icatibant with them gave them greater confidence in the management of their condition than they had had before self-administration training.

Discussion

This paper summarizes the first prospective evaluation of the efficacy, safety and tolerability of icatibant self-administration for acute attacks of HAE type III, in addition to HAE type I. Most symptoms improved rapidly following icatibant self-administration, with median times to first symptom improvement of 15 min (HAE type I) and 40 min (HAE type III). Complete symptom resolution occurred after medians of 5 h (HAE type I) and 24 h (HAE type III).

Although various studies of icatibant have assessed outcomes by slightly different methods and included different patient populations (limiting direct comparison), our data suggest that icatibant self-administration has similar efficacy to administration by HCPs. In three Phase III controlled

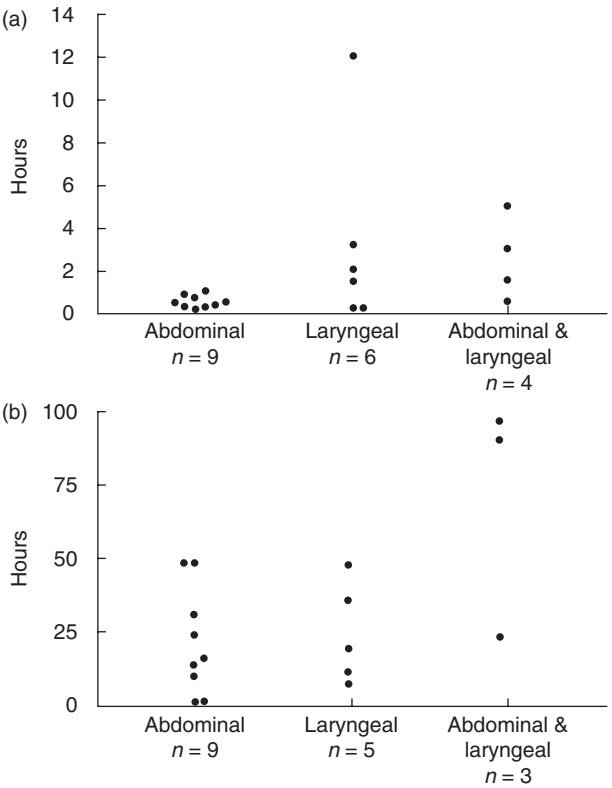

Fig. 2. Individual times to first symptom improvement (a) and complete resolution of symptoms (b) following icatibant self-administration in patients with hereditary angioedema (HAE) type III. Each data point represents one attack of HAE type III; *n*: number of evaluable attacks.

studies of HCP-administered icatibant in adults with acute abdominal and cutaneous attacks of HAE types I and II, median times to 'first improvement of the index symptom' were 0·8–1·5 h, and median times to 'clinically significant relief of the index symptom' were 2·0–8·0 h [12,13]. Our data are also consistent with interim findings from a Phase IIIB trial of icatibant self-administration in patients with HAE types I and II, in which the 'median time to onset of primary symptom relief' was 2 h [20].

In our study, most HAE attacks were self-treated successfully with one icatibant injection. Rescue medication usage was comparable to that reported in the controlled studies [12,13]. However, whereas in the present study up to three icatibant injections per attack were permitted, only one injection per attack was administered in the controlled studies, so rescue medication usage rates are not directly comparable.

Abdominal and laryngeal attacks were both treated effectively with self-administered icatibant. Notably, the time to first symptom improvement of 12 h for a single laryngeal attack in a patient with HAE type III appears to be an outlier (all other times to first symptom improvement for HAE type III laryngeal attacks were clustered at ≤3 h 10 min), and may have been related to the relatively long time between attack onset and icatibant self-administration (48 h). In another patient with HAE type III, complete symptom resolution occurred at 90 h and 96 h for two combined laryngeal/abdominal attacks (all other attacks resolved in ≤48 h), although each of these attacks needed only one injection of icatibant; the intervals between attack onset and icatibant self-administration were 72 h and 48 h, respectively.

Icatibant self-administration was generally well tolerated. Most patients experienced mild, spontaneously resolving ISRs, akin to the local tolerability reported for self- and HCP-administered icatibant; nevertheless, consistent with the established safety profile [12–15,20,21], no drug-related systemic adverse events occurred.

Patients who self-treated their attacks with icatibant reported being more confident about managing their condition than they were before self-administration training. Our findings reflect interim results of the prospective study of icatibant self-administration in patients with HAE types I and II, in which the majority of patients (94·6%) expressed a preference for self-injecting icatibant *versus* administration in a clinic, based on the convenience of carrying icatibant, ease of self-administration and satisfaction with symptom relief [22]. These data on patients' preference for icatibant self-administration are concordant with the HAE international home therapy consensus document recommendation that 'every patient should be considered for home therapy and self-administration training' [17].

Our investigation was limited by the absence of a comparator group. In addition, some patients did not record outcomes for every treated attack. Nevertheless, the reported improvements in patients' confidence in managing their condition, and the fact that no self-treated attacks required emergency hospitalization, are reassuring. Accordingly, these findings suggest that allowing patients the choice of icatibant self-administration, after appropriate training, has the potential to reduce the burden of HAE on hospital resources and lessen disruption of patients' everyday lives.

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Disclosure

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